REMARKS

Claims 16-29 and 31-44 are pending in the application as claims 1-15 are cancelled without prejudice or disclaimer. Claims 16-29 and 31-44 are amended to improve the grammar of certain claims and to remove multiple claim dependencies. The amendments are non-narrowing and no new matter has been introduced.

The objection of claims 4-7 under 37 C.F.R. § 1.75(c) is moot as these claims have been cancelled, and the objection to claims 19-22 under 37 C.F.R. § 1.75(c) is also moot because the amendments to these claims remove multiple claim dependencies. The rejections of claims 1-15 under 35 U.S.C. § 102(a) and 35 U.S.C. § 103(a) in view of Folkesson *et al.* also are moot in view of the cancellation of these claims.

Claims 1-29 and 31-44 were rejected under 35 U.S.C. § 112, second paragraph, as the term "indirect causes" is allegedly indefinite. The rejection is respectfully traversed. It is respectfully submitted that the term should be read in full context as "acute lung injury resulting from indirect causes which occur systemically and thereby injure the lung indirectly." This term provides a definite and accepted definition of a group of acute lung injuries known in the art. The systemic, indirect causes of acute lung injury are distinguished from direct causes on page 3, lines 17-27, and multiple indirect causes were well-characterized as of the filing date of the present application (*see e.g.* page 3, lines 19-22). Also, it was well known in the art that indirectly caused acute lung injuries differ substantially from directly caused injuries as described hereafter and in the preliminary amendment filed on May 29, 2002. In addition, U.S. Patent No. 6,190,872, which was cited in the Office action mailed July 2, 2002, demonstrates that these indirect and systemic causes of acute lung injury were well-known in the art (*see e.g.* column 1, lines 13-30). Thus, an injury defined by "acute lung injury resulting from indirect causes which occur systemically and thereby injure the lung indirectly" was well-defined as of the filing date of the present application, and therefore the language of claims 16-29 and 31-44 is definite and commensurate with the requirements of 35 U.S.C. § 112, second paragraph.

Claims 16-29 and 31-44 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Folkesson *et al.* and in view of Slotman (U.S. Patent No. 6,190,872). The Office cites Slotman for the alleged teaching that IL-8 was known as an inflammatory mediator of hypoxemia in acute lung injury resulting from indirect causes. The Office cites Folkesson *et al.* for the alleged teaching that IL-8 was critical for the development of lung injury and that neutralization of IL-8 provided a useful therapeutic treatment for acute lung injury. This rejection is respectfully traversed.

The experiments reported in Folkesson *et al.* are limited only to lung injury caused by acid inhalation, which is a direct cause. Slotman is limited to methods of diagnosing systemic inflammatory conditions, which are indirectly caused injuries, and does not teach or suggest diagnostic methods relating to directly caused inflammatory conditions. Slotman discloses no treatment methods. The systemic inflammatory conditions diagnosed in Slotman are characterized as being mediated by a wide variety of inflammatory mediators, listing more than seventeen (17) of these mediators as being causitive of the systemic inflammatory conditions (column 1, lines 22-30). While IL-8 is included in this list of potential mediators, the document does not teach or suggest that IL-8 is a prominent causative agent, and the document certainly does not teach or suggest methods for treating such conditions by neutralizing any of the listed mediators.

The pending claims are limited to treating hypoxemia in acute lung injury. As explained in the preliminary amendment filed April 15, 2002, the experiments reported in Folkesson *et al.* have no bearing on treating hypoxemia, which the Office recognized when it withdrew the rejection pertaining to claims 16-29 and 31-44. Because Slotman also fails to teach or suggest that an anti-IL-8 antibody is useful for treating hypoxemia in acute lung injury since it is directed to diagnostic methods, the cited combination does not result in the claimed subject matter.

It also is respectfully submitted that the Office does not fairly characterize the documents when it refers to their teachings as relating broadly to acute lung injuries. The Office should be sensitive to the cause of the lung injuries, as directly caused acute lung injuries are distinct from

systemic, indirectly caused acute lung injuries, as explained in the amendment filed September 13, 2001 and the preliminary amendment filed April 15, 2002. The specification notes that while aspiration, diffuse pulmonary infection, near drowning, inhalation of irritant gas, and lung contusion are causes of direct injury, indirect injury results from an entirely different set of causes, such as sepsis syndrome, severe non-thoracic trauma, hypertransfusion during emergency resuscitation, and artificial cardial pulmonary bypass surgery (*e.g.*, page 3, lines 17-22). Second, physicians classify acute respiratory distress syndrome resulting from direct causes as a different condition than acute respiratory distress syndrome resulting from indirect causes, as evidenced in Bernard *et al., Am. J. Respir. Crit. Care Med. Fall 149*: 818-824 (1994), which was forwarded to the Office on September 29, 2000. Thus, the cause of acute lung injury is important because directly caused acute lung injury is a distinct clinical condition as compared to systemic indirectly caused acute lung injury.

As further evidence that the two conditions are different, it was appreciated in the art that while one drug could have an effect on directly caused lung injuries, the drug can have no effect on lung injuries resulting from indirect causes. In particular, it was demonstrated that lidocaine could mitigate the affects of direct lung injury caused by acid aspiration, while on the other hand, the same drug had little effect on indirect lung injury caused by endotoxin infusion. This distinction between direct injury and indirect injury was reported in Nishina *et al.*, *Anesthesiology 88*: 1300-1309 (1998) and Nishina *et al.*, *Anesthesiology 83*: 169-177 (1995), which were forwarded to the Office on 27 September 2000. Hence, the directly caused injury and systemic indirectly caused injury are classified as two distinct conditions in the art and are clinically divergent.

Because the Slotman document is limited to indirectly caused inflammatory caused conditions and Folkesson *et al.* is limited to directly caused acute lung injury, the practitioner of ordinary skill in the art was not motivated to combine the teachings of these cited documents because the documents are drawn to clinically divergent conditions, and the teachings pertaining to one condition were not applicable to the other condition.

Another reason why there was no motivation to combine the cited documents was that the claimed methods were surprising in view of Slotman. While Slotman included IL-8 in its list of more than 17 effectors of systemic inflammatory conditions, the document never disclosed diagnostic methods in which IL-8 detection was determinative of systemic inflammatory conditions. There is nothing in Slotman that would have led the practitioner of ordinary skill to choose IL-8 from the more than 17 effector molecules listed, and Folkesson *et al.* provided no guidance because its experiments were limited to directly caused acute lung injury. Thus, it was surprising that the claimed methods of neutralizing just one of these many effector molecules could elicit a therapeutic effect on indirectly caused acute lung injury.

The distinctions between the directly caused and indirectly caused injuries also demonstrate that there was no reasonable expectation that neutralizing IL-8 with an antibody would successfully ameliorate symptoms of indirectly caused acute lung injury. Even though Folkesson *et al.* reported experiments in which an anti-IL-8 antibody ameliorated the effects of directly caused acute lung injury, there was no reasonable expectation that the antibody would affect symptoms of indirectly caused acute lung injury because drugs shown to be therapeutic for directly caused injuries were not effective for indirectly caused injuries, as demonstrated by Nishina *et al., supra.*

Accordingly, the cited combination failed to result in treatment of hypoxemia in acute lung injury as neither document taught or suggested methods for treating this condition. There was no motivation to combine the cited documents because Folkesson *et al.* and Slotman are directed to clinically divergent conditions and the results of the claimed methods were surprising. There also was no reasonable expectation for successfully treating indirectly caused acute lung injury using an IL-8 antibody because therapeutics for treating directly caused acute lung injuries were inapplicable to indirectly caused injuries. It is therefore respectfully requested that the Office withdraw the rejection under 35 U.S.C. § 103(a) as the pending claims are inventive and not *prima facie* obvious.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 350292000500.

Respectfully submitted,

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MARKED VERSION OF AMENDMENTS TO CLAIMS

In the Claims:

Please amend claims 16-29 and 31-44 as follows:

16. (Four Times Amended) A process for the production of a therapeutic agent for treatment of hypoxemia in acute lung injury resulting from indirect causes which occur systemically and thereby injure the lung indirectly, which comprises [comprising] mixing an anti-IL-8 antibody in an amount effective to treat the [acute lung injury] hypoxemia with a[n] pharmaceutical acceptable carrier.

17. (Twice Amended) A process according to claim 16 [in which], wherein the acute lung injury is acute respiratory distress syndrome.

18. (Twice Amended) A process according to claim 16 [in which], wherein the acute lung injury is adult respiratory distress syndrome.

19. (Twice Amended) A process according to [any of] claim[s] 16 [in which], wherein the indirect cause is [the] sepsis syndrome.

20. (Twice Amended) A process according to [any of] claim[s] 16 [in which], wherein the indirect cause is severe non-thoracic trauma.

21. (Twice Amended) A process according to [any of] claim[s] 16 [in which], wherein the indirect cause is hypertransfusion during emergency resuscitation.

22. (Twice Amended) A process according to [any of] claim[s] 16 [in which], wherein the indirect cause is an artificial cardiopulmonary bypass surgery.

23. (Twice Amended) A process according to claim 16, [in which] wherein the anti-IL-8 antibody is a monoclonal antibody.

24. (Twice Amended) A process according to claim 16, [in which] wherein the anti-IL-8 antibody is an antibody against mammalian IL-8.

25. (Twice Amended) A process according to claim 16, [in which] wherein the anti-IL-8 antibody is an antibody against human IL-8.

26. (Twice Amended) A process according to claim 16, [in which] wherein the anti-IL-8 antibody is the WS-4 antibody.

27. (Twice Amended) A process according to claim 16, [in which] wherein the anti-IL-8 antibody has the constant region of human antibody.

28. (Twice Amended) A process according to claim 16, [in which] wherein the anti-IL-8 antibody is a humanized or chimeric antibody.

29. (Twice Amended) A process according to claim 16, [in which] wherein the anti-IL-8 antibody is a humanized WS-4 antibody.

31. (Thrice Amended) A therapeutic method for treatment of hypoxemia in acute lung injury resulting from indirect causes which occur systemically and thereby injure the lung indirectly, which method comprises administering a composition comprising an anti-IL-8 antibody to a subject in need [said therapy] thereof.

32. (Amended) The method according to claim 31, wherein [in which] the acute lung injury is acute respiratory distress syndrome.

33. (Amended) The method according to claim 31, wherein [in which] the acute lung injury is adult respiratory distress syndrome.

34. (Twice Amended) The method according to [any one of] claim[s] 31, wherein [in which] the indirect cause is [the] sepsis syndrome.

35. (Twice Amended) The method according to [any one of] claim[s] 31, wherein [in which] the indirect cause is severe non-thoracic trauma.

36. (Twice Amended) The method according to [any one of] claim[s] 31, wherein [in which] the indirect cause is hypertransfusion during emergency resuscitation.

37. (Twice Amended) The method according to [any one of] claim[s] 31, wherein [in which] the indirect cause is an artificial cardiopulmonary bypass surgery.

38. (Twice Amended) The method according to claim 31, wherein [in which] the anti-IL-8 antibody is a monoclonal antibody.

39. (Amended) The method according to claim 31, wherein [in which] the anti-IL-8 antibody is an antibody against mammalian IL-8.

40. (Amended) The method according to claim 31, wherein [in which] the anti-IL-8 antibody is an antibody against human IL-8.

41. (Twice Amended) The method according to claim 31, wherein [in which] the anti-IL-8 antibody is the WS-4 antibody.

42. (Twice Amended) The method according to claim 31, wherein [in which] the anti-IL-8 antibody has the constant region of human antibody.

43. (Twice Amended) The method according to claim 31, wherein [in which] the anti-IL-8 antibody is a humanized or chimeric antibody.

44. (Twice Amended) The method according to claim 31, wherein [in which] the anti-IL-8 antibody is a humanized WS-4 antibody.